REMARKS

Claims 1-52 are pending in this application. Claims 1-15 and 33-46 have been withdrawn from consideration. Claims 16-32 and 47-52 are under examination. Claims 16-23 and 47-49 have been canceled without prejudice, solely to expedite prosecution (and not because Applicant agrees with any of the pending rejections). Claims 24, 32 and 52 have been amended to more particularly specify the invention. The amendments are supported throughout the specification; thus no new matter has been added.

Rejections Under 35 U.S.C. § 112, 2nd ¶

Claims 49 and 52 are rejected under 35 USC § 112, second paragraph for alleged indefiniteness for recitation of the phrase "like polyoxypropylene glycol…" Solely to expedite prosecution, Applicant has deleted this language from claim 52 and has canceled claim 49, obviating this rejection.

Rejections Under 35 U.S.C. § 102(b)

Claims 16, 17, 21-24, 28-32 and 47-52 were rejected under 35 USC § 102(b) for alleged anticipation by Schneider et al. EP 0554213 ("Schneider"). The Examiner asserts that Schneider teaches that vesicle suspensions or precursors thereof can be exposed to reduced pressure to evacuate one gas and then ambient pressure is restored with a second, desired gas and argues that this anticipates the claims 16, 17, 21-24, 28-32 and 47-52. Applicant respectfully disagrees.

As an initial matter, solely to expedite prosecution, Applicant has canceled claims 16-23 and 47-49, rendering the rejection as to these claims moot. The remaining claims require a sealed container for use in preparing a gas containing contrast agent for diagnostic imaging, said container comprising: 1) a dried material comprising at least one film forming surfactant; and 2) a gas wherein said gas is present at a pressure lower than atmospheric pressure. The claimed sealed container

contains a precursor to a contrast agent which comprises a dried material and a gas at a pressure lower than atmospheric pressure. The reduced pressure referred to in the description and in the relevant claims is the pressure of the gas in the precursor product before the container is mixed with a liquid to prepare an aqueous suspension of gas-filled microvesicles that is useful as a contrast agent. Once the claimed product is used to prepare the contrast agent, the whole content of the container (including the gas in the microvesicles) will necessarily be at atmospheric pressure (see page 31, lines 14-18). Thus, the sealed container stores the dried material in the presence of a gas at a pressure below atmospheric pressure.

In contrast, as the Examiner admits, Schneider teaches storing dry formulations under gas at ambient/atmospheric pressure. See Office Action at p. 3 ("Further, Schneider teaches that it is advantageous to store this dry powder under an atmosphere of a gas selected according to the invention (page 4, lines 39+).") Schneider does not teach or suggest a sealed container comprising a dried material comprising at least one film forming surfactant and a gas at lower than atmospheric pressure. The only disclosure in Schneider of use gas at reduced pressure is as an intermediate step in a process to replace a first gas with a second, desired gas, which is at ambient, not reduced pressure:

> For instance, the vesicle suspensions, or preferably precursors thereof (precursors here may mean the materials the microvesicle envelopes are made of, or the materials which, upon agitation with an aqueous carrier liquid, will generate or develop the formation of microbubbles in this liquid), can be exposed to reduced pressure to evacuate the gas to be removed and then the ambient pressure is restored with the desired gas for substitution.

Schneider, p. 4, lines 29-33 (emphasis added). During this replacement process, the container is not sealed as required by the instant claims. Indeed, Schneider makes clear that once the container is sealed for storage, the dried material is at ambient pressure "under an atmosphere of a gas selected according to the invention." Schneider, p. 4, lines 39-40.

Applicant notes that the pressure difference DP=P25-P75, mentioned by the Examiner and the critical pressure, Pc, mentioned in Schneider refer to external pressures applied to suspensions of microvesicles, to evaluate their resistance to said external pressure as a measure of stability. These values have no bearing on the pressure of the gas in the precursor product used to prepare the microvesicles (or, although irrelevant to the instant claims, on the pressure of the gas inside the microvesicles of the prepared contrast agent).

In sum, as Schneider fails to disclose a sealed container for use in preparing a gas containing contrast agent comprising a dried material comprising at least one film forming surfactant and a gas at lower than atmospheric pressure it cannot anticipate the claims.

Rejections Under 35 U.S.C. § 103(a)

Claims 16-32 and 47-52 were rejected under 35 U.S.C. § 103(a) for alleged obviousness over Schneider in view of Hugh D. Van Liew, J. App. Physiol. 82:2045-2053 (1997) ("Van Liew"). The Examiner admits that Schneider does not disclose the pressure ranges claimed in claims 18-20 and 25-27, but asserts that it "would have been obvious to one of ordinary skill in the art at the time the invention was to ensure that the pressure inside the gas microvesicles disclosed by Schneider and apply the knowledge that negative pressure inside the bubble to counter the tendency for outward diffusion of the gases disclosed by Hugh [Van Liew]." Office Action at 4. Applicant respectfully disagrees.

As explained above, Applicant's invention is directed to a precursor to a contrast agent. The claims are directed to a sealed container for use in preparing a gas containing contrast agent for diagnostic imaging, said container comprising: 1) a dried material comprising at least one film forming surfactant; and 2) a gas wherein said gas is present at a pressure lower than atmospheric pressure. The reduced pressure referred to in the description and in the relevant claims is the

pressure of the gas in the precursor product before the container is mixed with a liquid to prepare an aqueous suspension of gas-filled microvesicles that is useful as a contrast agent. Once the claimed product is used to prepare the contrast agent, the whole content of the container (including the gas in the bubbles) will necessarily be at atmospheric pressure (see page 31, lines 14-18). Thus, the claimed sealed container stores the dried material in the presence of a gas at a pressure below atmospheric pressure.

Neither of the cited references teaches or suggests such sealed containers. As explained above, Schneider does not disclose the claimed containers comprising dried material and a gas at a reduced pressure. All dry formulations in Schneider are stored under gas at atmospheric pressure – there is no suggestion to vary the pressure of the gas used in contrast agent precursor compositions, never mind a suggestion of the advantages of storing compositions under a gas at a pressure lower than atmospheric as in the claimed invention. Indeed, Schneider neither teaches nor suggests the surprising advantages of the claimed invention: that by storing the contrast agent precursor compositions at a reduced pressure, the storage life and stability of the compositions are extended, the size of the microvesicles generated using such precursors is consistently reproducible and independent of the amount of agitational energy applied and that such reconstituted suspensions have increased pressure resistance and thus improved stability in vivo. See e.g. US2005/0025710 at ¶ 0038-0042 and Examples.

The Van Liew article fails to remedy this deficiency. Like Schneider, the Van Liew article fails to teach or suggest sealed containers including contrast agent precursor compositions comprising dried materials and a gas at a pressure lower than atmospheric pressure. Indeed, Van Liew is directed to the properties of aqueous suspensions of microbubbles and does not even discuss precursor compositions used to prepare such suspensions. Thus, Van Liew cannot remedy the deficiencies of Schneider.

The Examiner asserts that Van Liew discloses bubbles with negative pressure inside, i.e. a pressure lower than the pressure in the surrounding medium. However, as explained above, the pressure of the gas inside the microbubbles after reconstitution is irrelevant to Applicant's claims, which are directed to sealed containers including precursor compositions used to prepare contrast agents. Moreover, as explained supra, once Applicant's claimed containers are used to generate microvesicle suspensions, those suspensions (both the microvesicles and the surrounding medium) are at atmospheric pressure.

Moreover, the Examiner's assertion appears to be based on a misinterpretation of the statement on page 2045 col. 2, lines 24 et seq..: "The crucial aspect of a structural stabilizer is that it must **produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside**, especially to counter the strong positive internal pressure due to surface tension when the bubbles are small". The phrase "negative pressure" in Van Liew does not refer to an "absolute" negative pressure (in the sense that the pressure inside the bubble is lower than the pressure in the surrounding medium, i.e. atmospheric pressure), but rather to a pressure which counters (i.e. having an opposite direction) the internal overpressure (with respect to the surrounding pressure) caused by surface tension at the gas-liquid interface.

This becomes clear by reading the subsequent mathematical explanation across page 2046. The presence of the stabilizer is intended to act as a counterpressure (P_T) against the hydrostatic pressure (P_γ) exerted by the surface tension (col. 2 first paragraph). Without the stabilizing layer, the gas contained in the bubble will be forced to diffuse outwardly, because of this hydrostatic pressure. The fact that the counterpressure exerted by the stabilizer is considered by the author a "negative pressure" (opposing to the "positive" hydrostatic pressure) is only a matter of mathematical convention, to indicate its direction with respect to the hydrostatic pressure, as inferable from equation 3 at the bottom of page 2046, col. 2. In said equation, the hydrostatic

pressure "P_i"appears as a positive value, while the counterpressure "P_I", generated by the stabilizer, is indicated as a negative pressure. Thus, the "negative" pressure generated by the stabilizer balances the hydrostatic pressure on the bubble, to avoid diffusion of the gas in the liquid – it does not mean that the pressure of the gas inside the bubble is lower than the pressure in the surrounding medium and it certainly does not teach or suggest storing contrast agent precursor compositions under a gas with a pressure lower than atmospheric. Indeed, there is no discussion of precursor compositions that may be used to generate microbubble suspensions ion Van Liew, never mind the advantages of the claimed compositions in sealed containers. Thus, even if one were to combine the teachings of Schneider with those of Van Liew, the skilled person would not have arrived at the instantly claimed invention, precluding a finding of obviousness.

The Double Patenting Rejections

Claims 16, 21-24, 28-32 and 47-52 remain rejected for alleged obviousness-type double patenting over US Patent Nos. 6485705, 6403057, 6896875, 6592846, 6613306, 6187288, 6042809, 5911972, 6183725 and 6136293 in view of the Van Liew article.

Claims 16, 21-24, 28-32 and 47-52 remain provisionally rejected for alleged obviousness-type double patenting over the claims of US Application Nos. 10/544123, 10/584327, 10/584,382, 10/725777, 10/831165, 11/058169, 11/202008, 11/660188, 11/851769 in view of the Van Liew article.

Applicant respectfully disagrees. Like Schneider, the cited patents and applications fail to teach or suggest the claimed contrast agent precursors comprising a dried material and a gas at reduced pressure. In each of the cited patents and applications, any precursor compositions used to prepare contrast agents are stored with a gas at atmospheric pressure, not the gas at reduced pressure

of the instant claims. Furthermore, none of the cited patents or applications teaches or suggests the advantages of employing gas at reduced pressure in contrast agent precursor compositions.

Moreover, as explained above, Van Liew, which neither teaches nor suggests contrast agent precursors, fails to remedy this deficiency. It too fails to teach or suggest use of gas at reduced pressure in contrast agent precursor compositions, never mind the advantages use of such reduced pressure gas provide: extended storage life and stability of the compositions, consistency and reproducibility in the size of the microvesicles generated using such precursors independent of the amount of agitational energy applied and increased pressure resistance and thus improved stability in vivo. See e.g. US2005/0025710 at ¶ 0038-0042 and Examples. In sum, the cited patents and applications cannot render Applicants claims obvious. Applicants request that the double patenting rejections be withdrawn.

CONCLUSION

Applicants submit that the pending claims are allowable. If any questions remain, Applicants invite the Examiner to contact Applicant's undersigned attorney who would welcome a chance to discuss the claims in a telephonic or in person interview.

No fees are believed due in connection with the filing of this response. However, the Director is hereby authorized to charge any required fees and credit any overpayments to Deposit Account No. 50-2168.

Respectfully submitted,

Dated: August 19, 2009

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